

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

In the matter of:

MAURICE LIPPMANN, M.D.
Regulatory Hearing

COMMISSIONER'S DECISION

The purpose of this proceeding is to determine, pursuant to 21 CFR 312.1(c)(1) and 21 CFR Part 16, whether Maurice Lippmann, M.D., a clinical investigator, will be disqualified from receiving investigational-use drugs. Associate Commissioner for Health Affairs Stuart Nightingale, M.D., presided over the regulatory hearing on January 13, 14, and 18, 1982. His recommendation is that Dr. Lippmann be disqualified.

I conclude that Dr. Lippmann repeatedly and deliberately failed to comply with regulations governing the conditions for exemption of new drugs for investigational use, and repeatedly and deliberately submitted false information to the sponsor. I also conclude that Dr. Lippmann has failed to provide adequate assurance that the conditions for exemption will be met in the future. Therefore, Dr. Lippmann is disqualified from receiving investigational new drugs. The reasons for my decision follow.

I. PROCEDURAL BACKGROUND

In 1978 and 1979 Dr. Lippmann conducted a study involving the analgesic drug _____ for _____ and a study involving the analgesic drug _____ for _____. Both studies were for the treatment of post-operative pain. In August and September 1979, the Food and Drug Administration ("FDA") audited the data generated by Dr. Lippmann's clinical investigations as part of its Bioresearch Monitoring Program. At the conclusion of those inspections, the National Center for Drugs and Biologics ("Center")^{1/}, FDA concluded that Dr. Lippmann had repeatedly or deliberately violated FDA regulations by failing to maintain adequate case histories. Consequently, on February 29, 1980, Frances O. Kelsey, Ph.D., M.D., Director of the Center's Division of Scientific Investigations, wrote to Dr. Lippmann and offered him an opportunity to attend an informal conference to discuss the alleged violations of FDA regulations. Dr. Lippmann initially responded in writing, dated April 28, 1980. On June 19, 1980, an informal conference was held at the Division of Scientific Investigations. Dr. Lippmann and his

^{1/} At the times of the inspections and hearing, the Bureau of Drugs was the complaining party. That Bureau is now the Office of Drugs in the Center.

legal counsel attended. Dr. Lippman supplemented his explanations after the conference, by letter dated August 21, 1980.

By letter dated July 21, 1981, the Associate Commissioner for Regulatory Affairs issued a notice to Dr. Lippmann providing him with an opportunity for a regulatory hearing under 21 CFR 16.24 and 312.1(c)(1). In addition to the allegation contained in Dr. Kelsey's February 29, 1980 letter, the notice alleged that Dr. Lippmann had repeatedly or deliberately submitted false information to the sponsor and had failed to obtain the informed consent of study subjects. The notice stated that, while neither of those allegations had been mentioned in Dr. Kelsey's letter, they arose from concerns expressed in that letter.

After hearing, the Presiding Officer, Dr. Nightingale, submitted his Report to me on February 4, 1983.

My decision is based on the administrative record. Under 21 CFR 16.80, the record includes the transcript of the hearing ("Tr."), the Report of the Presiding Officer ("Report"), the comments of the parties on that Report ("Comments"), the pre- and post-hearing statements submitted by the parties, the exhibits submitted by the parties, the assurances of Dr. Lippmann, and other relevant materials.

II. DECISION

I turn now to the merits of this proceeding. As I stated in my September 11, 1981 decision in In the Matter of Michael C. Gelfand, M.D., I must make two findings in order to conclude that a clinical investigator is no longer eligible to receive investigational new drugs. First, I must determine that the investigator has repeatedly or deliberately violated FDA regulations, or has repeatedly or deliberately submitted false information to the sponsor. Second, I must conclude that the clinical investigator has failed to furnish adequate assurance that the conditions of exemption will be met in the future. 21 CFR 312.1(c)(2).

A. VIOLATIONS OF FDA REGULATIONS

The Center's allegations and evidence concerning the and studies, and the Presiding Officer's findings, are closely parallel. I will address each allegation, as it pertains to both studies, in the order in which the Presiding Officer considered it. The Center has the burden of establishing the alleged violations by a preponderance of the evidence.

1. Concomitant Medication

The Presiding Officer found that Dr. Lippmann had failed to report accurately concomitant or other medication for nine of the 12 study subjects and 11 of the 15

study subjects whose records had been audited. The Presiding Officer concluded that Dr. Lippmann had failed to prepare and maintain adequate case histories for the two studies.^{2/} Dr. Lippmann's Comments are silent on this issue.

I agree with the Presiding Officer. This violation is a serious one. As I stated in my March 23, 1983 decision in In the Matter of Martin S. Mok, M.D., pages 10-11, it is imperative that the protocol's requirements concerning the exclusion and reporting of concomitant medication be meticulously followed. The failure to do so may affect the validity of the data and therefore the findings about the study drug's effectiveness.

In connection with the study, the Presiding Officer also found that Dr. Lippmann had submitted false information to the sponsor. He did not address this allegation in connection with the study. I find that Dr. Lippmann submitted false information to the sponsor of both studies.

^{2/} The study was a Phase 2 study for which Dr. Lippmann signed a Form FD-1572, which requires "adequate case histories." 21 CFR 312.1(a)(12) ¶6c). For the Phase 3 study, he signed a Form FD-1573, which requires "adequate and accurate case histories." 21 CFR 312.1(a)(13) ¶4c). Because there is no substantive difference between the two requirements, I will simply refer to "adequate case histories."

2. Significant Surgical Information

The Presiding Officer found that, for nine of 12 subjects and seven of 15 subjects, Dr. Lippmann had failed to report accurately significant surgical information. Hospital records and Dr. Lippmann's case histories for these 16 patients differed significantly on important information such as the date or type of surgery. The discrepancy in date of surgery was as great as 15 days. Report at 11 (Patient No. 73). In fact, according to hospital records, surgery was never performed on five of these patients. Report at 9-10 (Patient Nos. 1, 38, 45, 48) and 27 (Patient No. 10102) Accordingly, the Presiding Officer found that Dr. Lippmann had failed to maintain adequate case histories.

I agree with the Presiding Officer. Once again, Dr. Lippmann's Comments do not specifically address these discrepancies. He only suggests that some discrepancies may have arisen because the study nurse obtained some patient information for the case histories from a temporary hospital cardex rather than from permanent hospital records. Lippmann Comments at 6-7. Given the number of discrepancies and their magnitude, I do not find Dr. Lippmann's speculation about the possible source of error to be credible.

As with the allegations concerning concomitant medication, the Presiding Officer found that Dr. Lippmann had

submitted false information to the sponsor of the study, but failed to address the issue in connection with the study. I find that Dr. Lippmann submitted false information to the sponsor in connection with both studies.

3. Informed Consent

The Center presented the testimony of FDA Investigator Kenneth Nelson, who had interviewed 12 subjects and eight patients. Mr. Nelson testified that 18 of those patients had stated to him that the signatures on their consent forms were not in fact theirs, and that most of these persons did not recall being asked to participate in a drug study.

The Presiding Officer found that Dr. Lippmann had failed to obtain informed consent for these subjects, in violation of 21 CFR 312.1(a)(12) ¶6g) (study) and 21 CFR 312.1(a)(13) ¶4g) (study). He stated that the Center had presented convincing evidence that the patient signatures were false. He further stated that these were extremely serious violations because they constitute the gravest kind of misrepresentation. Report at 14.

I agree with the Presiding Officer. Dr. Lippmann's Comments do not address those findings of the Presiding Officer. Consistent with the Presiding Officer's finding, I also find that Dr. Lippmann submitted false

information to the sponsors by submitting consent forms with false patient signatures.

For each or study subject, Dr. Lippmann signed the consent form, under the following statement:

I certify that I have reviewed the contents of this form with the person signing above, who in my opinion, understood the explanation. I have explained the known side effects and benefits of the study. Any significant change in the nature of the study, from the described above, will be fully explained to the person signing above.

The Center urged, and the Presiding Officer adopted, the interpretation that by signing Dr. Lippmann had attested that he had personally participated in the consent process.

During the hearing, Dr. Lippmann testified that his study nurse actually had spoken with the patients and obtained the signatures, and that he had signed the forms subsequently in batches. Report at 15. On that basis, the Presiding Officer found that Dr. Lippmann had deliberately submitted false information to the study sponsors.

Dr. Lippmann's Comments attack that finding as being legally erroneous. He argues that the consent form should be interpreted in light of what he contends was accepted practice -- the study nurse obtains patient consent, while the investigator signs the form. Thus, he contends the effect of the Presiding Officer's Report is, contrary to

established agency law principles, to make him accountable for the actions of his nurse, but to deny him the ability to credit these actions as his own. He points out that the revised consent form now in use at the hospital where the studies were conducted permits either the investigator or his authorized representative to sign, attesting that the patient's consent was properly obtained.

I need not decide whether, by signing the certification statement on the consent forms when he had not personally obtained consent, Dr. Lippmann submitted false information to the sponsor because the certification statements were not literally true. I find that, even under Dr. Lippmann's interpretation of the consent form, he submitted false information to the sponsors, because neither he nor his nurse ever obtained consent.

4. Study Participation

The Center's evidence showed that two and three subjects were not in the hospital during the time they were reported by Dr. Lippmann to have participated in the studies, and that its investigation could not locate any hospital records at all for five and nine subjects. Investigator Nelson testified that he had interviewed study subjects and that nine and six subjects stated that they had not been asked to participate in a drug study. On the basis of this

evidence, the Presiding Officer found that Dr. Lippmann had failed to prepare adequate case histories and had submitted false information to the sponsor.

I agree with the Presiding Officer's finding. Once again, Dr. Lippmann does not address this issue in his Comments.

5. Charting of Study Drug

The Presiding Officer found that Dr. Lippmann had failed to record administration of the study drug in the hospital records of seven patients and 13 patients. He concluded that Dr. Lippmann had failed to keep adequate case histories and had submitted false information to the sponsors of the studies.

I agree with the Presiding Officer. As before, Dr. Lippmann's Comments are silent on this issue.

6. Deliberate Nature of the Violations

The Presiding Officer found that, with respect to the study, Dr. Lippmann's violations were deliberate. I agree that those violations were deliberate within the meaning and intent of the regulations.

The Presiding Officer did not address expressly whether the violations were deliberate. Reading his Report as a whole, I do not believe the facts warrant any distinction between the two sets of violations, or that the Presiding Officer intended to make such a distinction.

Accordingly, I find that the violations were also deliberate within the meaning and intent of the regulations.

7. Conclusions - and Studies

For the foregoing reasons, I conclude that the Center has met its burden of showing that Dr. Lippmann did not abide by FDA regulations. I conclude that Dr. Lippmann repeatedly and deliberately violated FDA regulations and repeatedly and deliberately submitted false information to the sponsors. Dr. Lippmann did so by failing to prepare adequate case histories and obtain informed consent.

B. ASSURANCES

I turn now to whether Dr. Lippmann has furnished adequate assurance that he will comply with the exempting regulations in the future. To avoid disqualification, Dr. Lippmann has the burden of establishing that his assurances are adequate. In Re Gelfand, page 18. As pointed out by the Presiding Officer, I need not accept assurances at face value. Rather, in considering whether assurances are adequate, I can take into account factors such as the seriousness of the violations as that reflects on the investigator's credibility. Report at 35.

Dr. Lippmann has provided a set of assurances, which are set forth at page 34 of the Presiding Officer's Report. The Presiding Officer concluded that Dr. Lippmann's assurances are not adequate. I agree with his conclusion.

The Presiding Officer found that Dr. Lippmann's testimony was not credible.^{3/} That finding is entitled to considerable weight, as the Presiding Officer saw and heard Dr. Lippmann's testimony. I conclude that the finding is amply supported by the record, and I adopt it as my own.

I also took into account the seriousness of the violations as it affects Dr. Lippmann's credibility. The Center's evidence, which was not contradicted to any significant degree, raised a strong inference that at least a significant portion of the two studies was never in fact done. That, of course, is a serious violation that affects the validity of the data generated. It could affect the safety of patients who receive the drugs in the future, because a decision to approve the drugs could be based in part on the results of those studies. Similarly, the manner in which patient consent was obtained could seriously affect the rights of patients.

^{3/} Section 16.60(f) of FDA's regulations pertaining to the conduct of a regulatory hearing requires the Presiding Officer to make a finding on witness credibility whenever credibility is a material issue. Here, there is no question that Dr. Lippmann's credibility is a material issue. Although he did not make a specific finding about Dr. Lippmann's credibility, it is implicit in the Report that the Presiding Officer did not find Dr. Lippmann to be credible.

Dr. Lippmann's assurances are made in the abstract and not in the context of a specific plan of investigation. In view of the serious nature of the violations under consideration, I believe it is not appropriate to accept only the general assurances proposed by Dr. Lippmann. In the Matter of Nathan S. Kline, page 32.

C. DR. LIPPMANN'S DEFENSES

I have already dealt with issues raised by Dr. Lippmann in his Comments as they relate to specific allegations. His remaining contentions are discussed below.

First, Dr. Lippmann contends that this proceeding is biased against him. Based on my review, I conclude that Dr. Lippmann's contention is without merit. Dr. Lippmann has received a fair and impartial hearing.

Dr. Lippmann contends that, at the outset, the Center deliberately concealed the true nature of the proceedings against him. He bases that allegation on the fact that he did not learn until the informal conference held in June 1980 that the Center was concerned that some patients had not actually participated in the studies. The Center's testimony showed that it had not made the allegation earlier because it was still under development. Tr. I-226-27. As noted in the Notice of Opportunity for Hearing, while some specific concerns were not framed in the Center's letter of February

1980, they arose from the same facts discussed in that letter. I believe the Center's handling of this proceeding has been reasonable and proper. Moreover, it is significant that Dr. Lippmann does not claim in his Comments that he was actually prejudiced in any way by the late addition of the allegations.

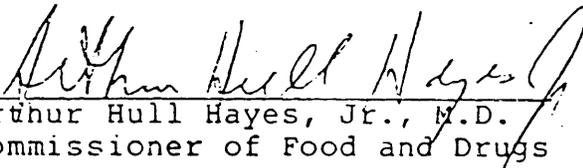
Dr. Lippmann attacks the credibility of Dr. Michael Hensley, a Center Medical Officer who participated in the audit of Dr. Lippmann's studies and testified at the hearing. He contends that three of the seven publications that Dr. Hensley listed on his curriculum vitae are misrepresented so as to inflate Dr. Hensley's credentials. Comments at 3-5. Dr. Lippmann is correct that the three citations are not accurate. While I do not condone Dr. Hensley's manner of compiling his publications list, I believe it is of no significance in this proceeding.

Dr. Lippmann contends that all problems with the two studies were the fault of his study nurse, and that his only failing was inadequate supervision and spot-checking of records. Lippmann Comments at 5-6. I have already stated my agreement with the Presiding Officer's finding that Dr. Lippmann's testimony was not credible. Further, accepting Dr. Lippmann's statements, he could nevertheless be disqualified for repeatedly violating FDA regulations and submitting false information to the sponsor. It goes without saying

that Dr. Lippmann bears ultimate responsibility for the proper conduct of the study and the actions of his associates. In Re Gelfand, page 11.

III. CONCLUSION

Dr. Lippmann has repeatedly and deliberately failed to abide by FDA regulations, and repeatedly and deliberately submitted false information to the sponsor. He has failed to furnish adequate assurance that he will comply with the regulations in the future. Accordingly, under 21 CFR 312.2(c)(2), I conclude that Dr. Lippmann is no longer eligible to receive investigational use drugs. Dr. Lippmann may in the future seek reinstatement of his eligibility to receive such drugs under 21 CFR 312.1(c)(6).


Arthur Hull Hayes, Jr., M.D.
Commissioner of Food and Drugs

Dated: May 30, 1983